REMARKS

I. STATUS OF THE CLAIMS

Claims 1-31 have been canceled. Claims 32-38 are pending in this application. Claim 32 has been amended to emphasize that Applicants' invention provides a stability-enhanced pharmaceutical formulation of the benzamide derivative of formula (1). Support for the amendments to claim 32 can be found in the specification at, for example, page 1, lines 27-36; page 2, lines 18-22; and page 17, lines 12-21. No new matter has been introduced by any of the amendments.

II. BRIEF SUMMARY OF APPLICANTS' INVENTION

Applicants disclose that while known benzamide therapeutic agents, such as those represented by formula (1), are stable *per se*, they become unstable and decompose markedly over time when combined with any of a number of commonly used, pharmaceutically acceptable excipients. Further, Applicants have noted that when these benzamide derivatives are formulated via a wet granulation process, which is the most common granulation method for preparing solid formulations, they become unstable and yield decomposition products in large quantities. Pharmaceutical formulations that employ ingredients commonly used for liquid preparations, such as polysorbates, polyethylene glycols and glycerin, were also found to result in destabilization of the benzamide derivatives of formula (1).

In response to these observations, Applicants have experimentally determined that, unexpectedly, several excipients actually enhance the formulation stability of the benzamide derivatives of formula (1). Table 1 (at page 11 of Applicants' specification) shows that while some excipients such as lactose, corn starch, crystalline cellulose, carmellose, light-weight silicic acid anhydride, magnesium aluminum metasilicate and titanium oxide accelerate the rate of decomposition of the benzamide derivative of formula (3) (*i.e.* compound 1) by varying degrees under both air-tight and open air conditions, other excipients such as D-mannitol, partially gelatinized starch, carmellose calcium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methyl cellulose and talc stabilize compound 1. Similarly, Table 5 shows that while typical pharmaceutically acceptable solvents polysorbate 80 and polyethylene glycol 400 degrade compound 1, dimethylacetamide and propylene glycol stabilize compound 1. Table 6

further shows that when the discovered stabilizing-enhancing compounds of the invention are added to a formulation of compound 1 with polyethylene glycol, the benzamide-degrading effects of the polyethylene glycol are significantly retarded.

III. THE REJECTION UNDER 35 U.S.C. § 102(b)

Claims 32, 33 and 35-38 have been rejected under 35 U.S.C. § 102(b) as being anticipated by EP 847 992 to Suzuki *et al.* ("*Suzuki*"). The Examiner maintains that *Suzuki* teaches in claim 14 the benzamide derivative claimed by Applicant along with several of the same generally used diluents or excipients (*e.g.*, binders, extenders, fillers, moisturizers, disintegrants, surfactants and lubricants) claimed by Applicants. In addition, according to the Examiner, *Suzuki* also teaches the pharmaceutical dosage form of Applicants' invention.

Applicants respectfully disagree with the Examiner's assessment of the novelty of Applicants' invention. The list of stability-enhancing compounds in claim 32 is limited to a specific group consisting of D-mannitol, sodium carboxymethyl starch, hydroxypropyl cellulose, magnesium stearate, partly pregelatinized starch, hydroxypropylmethyl cellulose, dimethylacetamide, sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, ammonia, monosodium fumarate, sodium dehydroacetate, sodium erythorbate, trisodium citrate and an amino compound. *Suzuki* does not specifically disclose any of these compounds anywhere in the specification. For example, while *Suzuki* discloses starch, it does not disclose specifically a partly pregelatinized starch. Similarly, while stearates, as a class of compounds are disclosed, magnesium stearate is not specifically disclosed.

The Examiner appears to find anticipation of Applicants' specifically recited excipients through *Suzuki*'s broad disclosure of generally used diluents or excipients such as binders, extenders, fillers, moisturizers, disintegrants, surfactants, and lubricants. As MPEP § 2131.03 indicates, if the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute anticipation of the claims. "The unexpected results may also render the claims unobvious." Applicants believe that the fact that several of the excipients disclosed by *Suzuki* (*e.g.* lactose,

crystalline cellulose, polyethylene glycol, *etc.*) have been shown by Applicants to undesirably accelerate the degradation of benzamide derivatives provides further evidence of the novelty of Applicants' stability-enhanced formulations. Because *Suzuki* does not teach each and every limitation of Applicants' claim 32, *Suzuki* cannot anticipate claim 32 and Applicants respectfully request that this rejection be withdrawn.

IV. THE REJECTION UNDER 35 U.S.C. § 103(a)

Claim 34 is rejected as being obvious over *Suzuki* in view of the International Cosmetic Ingredient Dictionary and Handbook ("*Dictionary*"). The Examiner states that *Suzuki* does not teach the inclusion of each of the specific excipients claimed by Applicants but that the *Dictionary* may be relied upon for teaching the excipients that are not disclosed by *Suzuki*, such as mannitol, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or amino compounds. According to the Examiner, one skilled in the art would have been motivated to include the well known excipients taught by the *Dictionary* in the compositions described by *Suzuki*.

As discussed in Section II above, Applicants have discovered that the presence of various excipients in formulations containing benzamide derivatives actually enhance the stability of the benzamide derivatives while other excipients accelerate the degradation of benzamide derivatives. However, both *Suzuki* and the *Dictionary* lump together several classes of excipients and do not teach or suggest differentiating these compounds based on their individual, sometimes dramatically different, effects on the stability of benzamide derivatives.

In contrast, Applicants have demonstrated, for example, that the sugar lactose accelerates degradation of a benzamide derivative while another sugar, D-mannitol, enhances stability of the same benzamide derivative (see Table 1 in Applicant's specification). Similarly, one type of starch, partly pregelatinized starch, stabilizes a benzamide derivative while another type of starch, corn starch, destabilizes the same benzamide derivative (see Table 1). Further, one type of cellulose, *e.g.*, crystalline cellulose, degrades a benzamide derivative while other celluloses, *e.g.*, hydroxypropyl cellulose and hydroxypropylmethyl cellulose, enhance the stability of the same benzamide.

Neither *Suzuki* nor the *Dictionary* teach or suggest the additive effects of various excipients. In contrast, Applicants demonstrate, for example, in Table 6 of the specification that

certain specific compounds, when added to a benzamide-polyethylene glycol formulation, can counteract the benzamide-degrading properties of the polyethylene glycol. A person of ordinary skill in the art would not be motivated, after a reading of *Suzuki* and the *Dictionary*, to choose some excipients for their benzamide-stability-promoting properties and to avoid other excipients for their benzamide-degrading properties.

The Examiner states that sodium bicarbonate, disodium phosphate and potassium bicarbonate, as well as amino compounds, are all well-known pH adjusters taught by the *Dictionary* and thus would be obvious to use in Applicants' invention. Applicants note that the adjustment of pH is only meaningful in aqueous solutions. In contrast, Applicants have demonstrated that several amino compounds, along with other non-amino compounds, enhance the stability of select benzamide derivatives. If pH were the only factor involved in stability, then benzamide compound 1, which itself is an amino compound, would not degrade in formulations with neutral excipients such as lactose. Table 1 shows that this is clearly not the case. Therefore, it would appear that the amino compounds are operating to stabilize benzamides by mechanisms other than pH adjustment. For at least the reasons discussed above, the *Dictionary* cannot remedy the deficiencies present in *Suzuki* and thus, Applicants request that this rejection be withdrawn.

V. CONCLUSION

Upon consideration of the foregoing, it will be recognized that Applicants have fully and appropriately responded to all of the Examiner's objections. The amendments to the claims are fully supported by the specification and do not add new matter. Accordingly, the claims are believed to be in proper form in all respects and allowable.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTION PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

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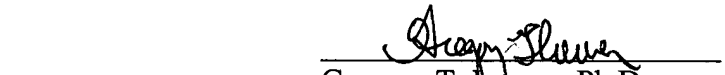

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